UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,663	08/01/2003	Alena Donda	NY-LUD 5673.1-US	3562

24972 7590 05/19/2006

FULBRIGHT & JAWORSKI, LLP
666 FIFTH AVE
NEW YORK, NY 10103-3198

EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,663	DONDA ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2006 and 29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed 3/9/06 and Applicant's response filed 3/29/04 are acknowledged and have been entered.

2. Applicant's election of the species of A is a Fab' fragment specific for CEA, B is bis maleimide polyethylene oxide, and C is one HLA-A2 molecule complexed with SEQ ID NO: 1 (influenza peptide GILGFVFTL) in Applicant's said amendment and response is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1, 3, 4, 9 and 15 read on the elected species.

Upon consideration of the prior art, the search has been extended to include the species "antibody" recited in instant claim 8, the species of claim 2 wherein B is absent and n is 1, and the species "tumor rejection antigen" recited in instant claim 14.

Accordingly, claims 5-7 and 10-13 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-4, 8, 9, 14 and 15 are presently being examined.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP 602.01 and 602.02.

The oath or declaration is defective because: the filing date of the 10/276,764 parent application is listed as 11/19/02, whereas the filing date is 2/10/03. In addition, the PCT/US01/17184 priority document is not listed in the declaration.

4. The drawings filed 11/19/02 are objected to because the Y-Axis values for Figures 2B and 3B are obscured by the Y-Axis Labels. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet

submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the Examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

5. If Applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, 121 or 365(c), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (*i.e.,* continuation, divisional, or continuation-in-part) of the applications.

It is noted by the Examiner that the first line of the specification references Serial No. 10/276,764, however, the filing date is listed as 11/19/02, whereas it should be listed as 2/10/03. In addition, Applicant has not made reference to PCT/US01/17184.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-3, 8, 9 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Ogg *et al* (Brit. J. Cancer, 3/1/00, Vol. 82, No. 5, pages 1058-1062).

Ogg *et al* teach conjugating a tumor-specific antibody to an MHC class I/peptide complex to make a conjugate prior to administration *in vivo* (especially page 1061, column 1, third full paragraph). Ogg *et al* teach that the antigen binding site of the antibody should contact the tumor cell surface antigen, whereas the MHC class I molecule should be attached to the antibody at the C-terminal end of the antibody. Ogg *et al* also exemplify making a conjugate using avidin-biotin, wherein the antibody is attached to two biotinylated MHC molecules (HLA-A2.1). Ogg *et al* further teach that the peptide may be a viral antigenic peptide from the HIV gag protein or a viral antigenic peptide from EBV (especially Figure 1, materials and methods, last paragraph at column 1 on page 1058 and first full paragraph at column 2 on page 1061).

8. Claims 1-3, 8, 9, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/64464 A2.

WO 99/64464 A2 teaches the conjugate of the instant claims consisting of an MHC/peptide ("C") complex linked to a tumor specific monoclonal antibody such as an anti-CEA antibody ("A") via avidin/biotin ("B"). WO 99/64464 A2 teaches that the MHC class I molecule may be HLA-A2.1 and the peptide should be chosen that can induce a powerful immune response or that it has a strong CTL response against it. WO 99/64464 A2 teaches that it is preferable that the peptide should be one against which the patient is likely to have had previous exposure, such as the EBV RAKFFQLL peptide or a viral peptide such as an influenza virus peptide, but that it may also be a tumor specific peptide. WO 99/64464 A2 also teaches direct linkage of the MHC/peptide complex to the antibody (see entire article, especially abstract, Figure 1, claims, page 6 at lines 9-18, paragraph spanning pages 6-7, paragraph spanning pages 8-9).

9. Claims 1-3, 8, 9 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2003/0166277 A1.

US 2003/0166277 A1 discloses one or more MHC/peptide complexes linked directly to an antibody at the C-terminus of the antibody, that the antibody may be specific for a cell surface marker of a tumor cell, such as the CEA antigen on tumor cells, that the antibody may be an antibody fragment that binds antigen, such as Fab, F(ab')2, Fv or scFv. US 2003/0166277 A1 also discloses wherein the MHC/peptide complex(es) may be linked to the antibody via avidin-biotin. US 2003/0166277 A1 discloses redirecting specific T cell activity to tumor cells through antibody targeted peptide/MHC complexes, an example of which is a tumor-specific antibody linked to a peptide/MHC complex, wherein the peptide is the immunodominant influenza matrix peptide 58-66/HLA-A2.1. US 2003/0166277 A1 discloses that the immune response to commonly encountered pathogens such as influenza virus is associated with a high frequency of high avidity T cells that are specific for the immunodominant peptide/MHC complexes of cells infected with these pathogens. US 2003/0166277 A1 discloses that these same highly represented, high affinity T cells can be redirected to tumors by linking the dominant peptide/MHC recognized by these T cells to a tumor specific antibody specificity. US 2003/0166277 A1 discloses that the antigenic peptide may also be from a tumor specific antigen. US 2003/0166277 A1 discloses that direct fusion of the antibody to the MHC/peptide complex simplifies production, and discloses methodologies for direct linkage, as well as for other types of linkage (especially abstract, [0012], [0014], [0015], [0027], [0028], [0031], [0055], Tables 1-4, [0072], [0073], [0084], [0098], [0101]-[0108], [0111], [0115], [0121], [0244], Figure 1, claims).

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-4, 8, 9, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0166277 A1 in view of US Patent No. 5,670,132.

US 2003/0166277 A1 discloses one or more MHC/peptide complexes linked directly to an antibody at the C-terminus of the antibody, that the antibody may be specific for a cell surface marker of a tumor cell, such as the CEA antigen on tumor cells, that the antibody may be an antibody fragment that binds antigen, such as Fab, F(ab')2, Fv or scFv. US 2003/0166277 A1 also discloses wherein the MHC/peptide complex(es) may be linked to the antibody via avidin-biotin. US 2003/0166277 A1 discloses redirecting specific T cell activity to tumor cells through antibody targeted peptide/MHC complexes, an example of which is a tumor-specific antibody linked to a peptide/MHC complex, wherein the peptide is the immunodominant influenza matrix peptide 58-66/HLA-A2.1. US 2003/0166277 A1 discloses that the immune response to commonly encountered pathogens such as influenza virus is associated with a high frequency of high avidity T cells that are specific for the immunodominant peptide/MHC complexes of cells infected with these pathogens. US 2003/0166277 A1 discloses that these same highly represented, high affinity T cells can be redirected to tumors by linking the dominant peptide/MHC recognized by these T cells to a tumor specific antibody specificity. US 2003/0166277 A1 discloses that the antigenic peptide may also be from a tumor specific antigen. US 2003/0166277 A1 discloses that direct fusion of the antibody to the MHC/peptide complex simplifies production, and discloses methodologies for direct linkage, as well as for other types of linkage (especially abstract, [0012], [0014], [0015], [0027], [0028], [0031], [0055], Tables 1-4, [0072], [0073], [0084], [0098], [0101]-[0108], [0111], [0115], [0121], [0244], Figure 1, claims).

US 2003/0166277 A1 does not disclose wherein the antibody fragment is Fab'.

US Patent No. 5,670,132 discloses that antibody fragments such as Fab', Fab, $F(ab')_2$ and $F(ab)_2$have faster targeting kinetics than intact immunoglobulin and offer the advantage of including a much lower occurrence of human immune responses compared to intact IgG molecules.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used any antigen binding antibody fragment such as disclosed by US 2003/0166277 A1 such as the Fab' fragment disclosed by US Patent No. 5,670,132 in the antibody-MHC/peptide conjugate disclosed by US 2003/0166277 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make an antibody-MHC/peptide conjugate such as disclosed by US 2003/0166277 A1 but using an antibody fragment such as disclosed by US Patent No. 5,670,132 that has the advantage of faster targeting kinetics and lower occurrence of human immune responses compared to intact IgG antibody molecules.

12. Claims 1-4, 8, 9, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0166277 A1 in view of Delgado *et al* (Brit. J. Cancer. 1996, Vol. 73, pages 175-182).

US 2003/0166277 A1 discloses one or more MHC/peptide complexes linked directly to an antibody at the C-terminus of the antibody, that the antibody may be specific for a cell surface marker of a tumor cell, such as the CEA antigen on tumor cells, that the antibody may be an antibody fragment that binds antigen, such as Fab, F(ab')2, Fv or scFv. US 2003/0166277 A1 also discloses wherein the MHC/peptide complex(es) may be linked to the antibody via avidin-biotin. US 2003/0166277 A1 discloses redirecting specific T cell activity to tumor cells through antibody targeted peptide/MHC complexes, an example of which is a tumor-specific antibody linked to a peptide/MHC complex, wherein the peptide is the immunodominant influenza matrix peptide 58-66/HLA-A2.1. US 2003/0166277 A1 discloses that the immune response to commonly encountered pathogens such as influenza virus is associated with a high frequency of high avidity T cells that are specific for the immunodominant peptide/MHC complexes of cells infected with these pathogens. US 2003/0166277 A1 discloses that these same highly represented, high affinity T cells can be redirected to tumors by linking the dominant peptide/MHC recognized by these T cells to a tumor specific antibody specificity. US 2003/0166277 A1 discloses that the antigenic peptide may also be from a tumor specific antigen and that the MHC/peptide complex. US 2003/0166277 A1 discloses that direct fusion of the antibody to the MHC/peptide complex simplifies production, and discloses methodologies for direct linkage, as well as for other types of linkage (especially abstract, [0012], [0014], [0015], [0027], [0028], [0031], [0055], Tables 1-4, [0072], [0073], [0084], [0098], [0101]-[0108], [0111], [0115], [0121], [0244], Figure 1, claims).

US 2003/0166277 A1 does not disclose wherein the antibody fragment is Fab'.

Delgado *et al* teach that use of a Fab' fragment (F9) of an anti-CEA antibody (A5B7) superior to use of the intact antibody or use of the $F(ab')_2$ fragment, and may be useful in a conjugate for immunotherapy and tumor imaging (especially abstract and discussion).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used any antigen binding antibody fragment such as taught by US 2003/0166277 A1 such as the Fab' fragment taught by Delgado *et al* in the antibody-MHC/peptide conjugate disclosed by US 2003/0166277 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make an antibody-MHC/peptide conjugate such as disclosed by US 2003/0166277 A1 but using an antibody fragment such as taught by Delgado *et al* that is superior to use of the intact antibody or use of the $F(ab')_2$ fragment as taught by Delgado *et al.*

13. Claims 1-4, 8, 9, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ogg *et al* (Brit. J. Cancer, 3/1/00, Vol. 82, No. 5, pages 1058-1062) in view of US Patent No. 5,670,132, Delgado *et al* (Brit. J. Cancer. 1996, Vol. 73, pages 175-182) and Hoffman *et al* (Cytometry. 11/00, Vol. 41, pages 321-328).

Ogg *et al* teach conjugating a tumor-specific antibody to an MHC class I/peptide complex to make a conjugate prior to administration *in vivo* (especially page 1061, column 1, third full paragraph). Ogg *et al* teach that the antigen binding site of the antibody should contact the tumor cell surface antigen, whereas the MHC class I molecule should be attached to the antibody at the C-terminal end of the antibody. Ogg *et al* also exemplify making a conjugate using avidin-biotin, wherein the antibody is attached to two biotinylated MHC molecules (HLA-A2.1). Ogg *et al* further teach that the peptide may be a viral antigenic peptide from the HIV gag protein or a viral antigenic peptide from EBV. Ogg *et al* teach that a number of cell surface molecules with specificity to tumor cells have been identified and mAb to some of these antigens have been used for targeting tumor cells in vivo. Ogg *et al* teach that they have sought to link the powerful effector mechanisms of CTL with the specificity of mAb, by targeting recombinant HLA class I molecules to tumor cells using an antibody delivery system, the MHC being HLA-A2.1 refolded around an immunodominant viral peptide. Ogg *et al* further teach that the peptide may be a viral antigenic peptide from the HIV gag protein or a viral antigenic peptide from EBV. Ogg *et al* teach that the EBV peptide is better for use than the HIV peptide for *in vivo* application because CTL specific for the EBV peptide can account for up to 44% of peripheral blood CTL in the acute phase, and because anti-EBV CTL response persists at significant levels for years after primary infection and may repeatedly be re-activated during life, thus providing natural boosts in the frequency and activation of CTL that might be re-targeted at tumors (especially abstract, last paragraph at column 1 on page 1058 and first full paragraph at column 2 on page 1061).

Ogg *et al* do not teach wherein the antibody portion is an antigen-binding antibody fragment such as Fab', nor wherein the viral peptide is GILGFVFTL (M1 58-66), the immunodominant influenza matrix 58-66 peptide, nor wherein the antibody specificity is anti-CEA.

US Patent No. 5,670,132 discloses that antibody fragments such as Fab', Fab, $F(ab')_2$ and $F(ab)_2$have faster targeting kinetics than intact immunoglobulin and offer the advantage of including a much lower occurrence of human immune responses compared to intact IgG molecules.

Delgado *et al* teach that use of a Fab' fragment (F9) of an antibody (A5B7) with specificity for CEA tumor cell antigen is superior to use of the intact antibody or the $F(ab')_2$ fragment, and may be useful in a conjugate with PEG (used to increase half-life in circulation of the Fab' fragment) in immunotherapy and tumor imaging (especially abstract and discussion).

Hoffman *et al* teach that the GILGFVFTL peptide is the influenza matrix immunodominant peptide, amino acid residues 58-66, and that it is a recall antigenic peptide, *i.e.,* high affinity memory T cells exist in persons previously infected with influenza (especially page 322 at column 2, second full paragraph, abstract and introduction).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted for the antibody in the conjugate taught by Ogg *et al* , an antigen binding antibody fragment disclosed by US Patent No. 5,670,132 such as the anti-CEA Fab' taught by Delgado *et al*, and to have used any HLA-A2.1 immunodominant viral peptide that is a recall peptide such as the M1 58-66 peptide taught by Hoffman *et al* or the EBV peptide taught by Ogg *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make an antibody-MHC/peptide conjugate such as taught by Ogg *et al* but using an antibody fragment such as disclosed by US Patent No. 5,670,132 that has the advantage of faster targeting kinetics and lower occurrence of human immune responses compared to intact IgG antibody molecules such as the anti-CEA Fab' antibody fragment taught by Delgado *et al*. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Hoffman *et al* teach the M1 58-66 peptide is a recall peptide to a common viral infectant, and Ogg *et al* teach it is advantageous to use a recall peptide such as the EBV peptide.

14. Claims 1-4, 8, 9, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/64464 A2 in view of US Patent No. 5,670,132, Delgado *et al* (Brit. J. Cancer. 1996, Vol. 73, pages 175-182), and Hoffman *et al* (Cytometry. 11/00, Vol. 41, pages 321-328).

WO 99/64464 A2 teaches the conjugate of the instant claims consisting of an MHC/peptide ("C") complex linked to a tumor specific monoclonal antibody such as an anti-CEA antibody ("A") via avidin/biotin ("B"). WO 99/64464 A2 teaches that the MHC class I molecule may be HLA-A2.1 and a peptide should be chosen that can induce a powerful immune response or that has a strong CTL response against it. WO 99/64464 A2 teaches that it is preferable that the peptide should be one against which the patient is likely to have had previous exposure, such as the EBV RAKFFQLL peptide or a viral peptide such as an influenza virus peptide, but that it may also be a tumor specific peptide. WO 99/64464 A2 also teaches direct linkage of the MHC/peptide complex to

the antibody (see entire article, especially abstract, Figure 1, claims, page 6 at lines 9-18, paragraph spanning pages 6-7, paragraph spanning pages 8-9).

WO 99/64464 A2 does not teach wherein the antibody portion is an antigen-binding antibody fragment such as Fab', nor wherein the viral peptide is GILGFVFTL (M1 58-66), the immunodominant influenza matrix 58-66 peptide.

US Patent No. 5,670,132 discloses that antibody fragments such as Fab', Fab, $F(ab')_2$ and $F(ab)_2$have faster targeting kinetics than intact immunoglobulin and offer the advantage of including a much lower occurrence of human immune responses compared to intact IgG molecules.

Delgado *et al* teach that use of a Fab' fragment (F9) of an antibody (A5B7) with specificity for CEA tumor cell antigen is superior to use of the intact antibody or the $F(ab')_2$ fragment, and may be useful in a conjugate with PEG (used to increase half-life in circulation of the Fab' fragment) in immunotherapy and tumor imaging (especially abstract and discussion).

Hoffman *et al* teach that the GILGFVFTL peptide is the influenza matrix immunodominant peptide, amino acid residues 58-66, and that it is a recall antigenic peptide, *i.e.*, high affinity memory T cells exist in persons previously infected with influenza (especially page 322 at column 2, second full paragraph, abstract and introduction).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted for the antibody in the conjugate taught by WO 99/64464 A2, an antigen binding antibody fragment disclosed by US Patent No. 5,670,132 such as the anti-CEA Fab' taught by Delgado *et al*, and to have used any HLA-A2.1 immunodominant viral peptide that is a recall peptide such as the M1 58-66 peptide taught by Hoffman *et al* or the EBV peptide taught by WO 99/64464 A2.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make an antibody-MHC/peptide conjugate such as taught by WO 99/64464 A2 but using an antibody fragment such as disclosed by US Patent No. 5,670,132 that has the advantage of faster targeting kinetics and lower occurrence of human immune responses compared to intact IgG antibody molecules. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Hoffman *et al* teach the M1 58-66 peptide is a recall peptide to a common viral infectant, and WO 99/64464 A2 teaches it is advantageous to use a recall peptide.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-4, 8, 9, 14 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8 and 12-15 of copending Application No. 10/276,764 in view of WO 99/64464 A2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the component "B" in base claim 1 of the instant application may be optionally present. In addition, WO 99/64464 A2 teaches complexes that include component "B" of the instant claims, *i.e.,* for example, avidin/biotin, as enunciated at item #8 of this Action. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have connected the antibody/fragment thereof component "A" to the MHC/peptide component "C" of the claims of '764 using the avidin/biotin "B" component taught by WO 99/64464 A2. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 99/64464 A2 teaches that the avidin/biotin system forms a stable bridge between the components, and the bridged conjugate is an obvious variant.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-4, 8, 9, 14 and 15 are directed to an invention not patentably distinct from claims 1-4, 8 and 12-15 of commonly assigned 10/276,764, as enunciated above at item #16 of this Action.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/632,663, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

18. No claim is allowed.

19. There is a spelling error in the abstract: there should be a comma between "cells" and "b" at line 4.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640/Technology Center 1600
May 12, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600